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EXAMINER
SPIEGLER, ALEXANDER H

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/618,129	WANG, XIAO BING	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 1st, 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9 and 11-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-9 and 11-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 1st, 2002 has been entered.

Currently, claims 2-9 and 11-37 are pending. All arguments have been full considered and thoroughly reviewed, but are deemed not persuasive for the reasons, which follow. This action is made NON-FINAL. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 2-9 and 11-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 2-9 and 11-37 are indefinite over "the other type of nucleotide" because this lacks antecedent basis. It is not clear what "the other type of nucleotide" is referring to.

B) Claims 2-9 and 11-37 are indefinite over "labeled nucleotides incorporated into a primer" and "preparing an unlabeled primer" because it is not clear as to whether or not the primer is labeled.

C) Claims 2-9 and 11-37 are indefinite over "high stringency conditions" because it is not clear as to what conditions constitute "high stringency conditions". Applicants should amend the claims to include the specific washing conditions.

D) Claims 2-9 and 11-37 are indefinite over "the target nucleotide" because this lacks antecedent basis. Applicants can overcome this rejection by adding "base" after "nucleotide".

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 2-9, 11-15 and 23-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Applied Genetics (WO 96/30545).

Applied Genetics ("AG '545") teaches a method of detecting a target nucleic acid performing a primer extension reaction in the presence of three non-terminators (abstract, pgs. 16 and 58, Table 1A and B). The mutation can be any variant (pg. 14), the terminator is a dideoxynucleotide (pg. 6), the non-terminators and terminators may be labeled (pgs. 12-13).

Response to Applicants Arguments

Applicants arguments have been considered, but are not persuasive because AG '545 **does** teach the limitations that Applicants contend are not present in the disclosure of Ag '545.

1) Applicants argue that the primers of AG '545 are labeled, which is inconsistent to the present invention.

However, AG '545 teaches,

"The primer is preferably designed to satisfy at least two criteria...that the primer be capable of specifically hybridizing to the target nucleic acid" and "that the primer is hybridized proximal and 3' to the point of deviation...by 'proximal' is meant...most preferably 0 to 3 nucleotides exist between the 3' end of the primer and the point of deviation between the related nucleotides". (pg. 18).

Here, the AG '545 teaches the only criteria for the primers (which does not include a label). Additionally, the disclosure teaches and suggests that the primer is not labeled (pg. 21, ln. 27-31) and is further evidenced in claim 1, which specifically does not require a label (pg. 58).

2) Applicants argue that present invention relies on the primer being immediately adjacent (i.e. downstream) of the 3' end of the primer.

However, AG '545 teaches this limitation: "the primer is hybridized proximal and 3' to the point of deviation...by 'proximal' is meant...most preferably **0 to 3 nucleotides exist between the 3' end of the primer and the point of deviation** between the related nucleotides" (pg. 18). Figure 1 also demonstrates that the deviation is downstream of the 3' end of the primer.

3) Applicants argue that AG '545 teaches the use of more than one terminator, whereas the instant invention is directed to a method wherein only one type of terminator is used.

First, it is noted that the use of a terminator is "optionally" in the instant claims. Ag '545 teaches the use of three non-terminators and no terminators (for example on page 8, ln. 4-6 and claim 22 on page 61), or the combination of three non-terminators and one terminator (abstract, pgs. 8, 16, 18-19, 61, and Table 1A and B).

4) Applicants argue that AG '545 does not teach that the dNTPs are labeled and the ddNTP's are not labeled.

First, it is noted that the use of a terminator is "optionally" in the instant claims, thus, requiring only that of the three non-terminators, only one must be labeled. Ag '545 teaches Ag

'545 teaches the use of three non-terminators and no terminators (for example on page 8, ln. 4-6 and claim 22 on page 61), specifically, claim 23 on page 61, teaches the use of three non-terminators, wherein one non-terminator is labeled.

Furthermore, AG '545 teaches: "it is contemplated that the nucleotides used for extension [i.e. non-terminators] **or** chain termination include detection moieties" (pg. 21, ln. 28-30). This teaching provides support for the possibility of three non-terminators and one terminator, wherein one non-terminator is labeled. Since it is clear that the invention contemplates three non-terminators and one terminator (pg. 8, ln. 1-4 and pg. 16, ln. 27-28), and that the non-terminator can be labeled, whereas the terminator is not labeled (pg. 21, ln. 28-30).

5) Applicants argue that AG '545 requires gel electrophoresis, whereas the present invention does not employ gel electrophoresis.

However, AG '545 teaches that mass spectroscopy can be used in the detection without using gel electrophoresis (pg. 21, ln. 7).

Therefore, Applicants have not overcome the prior art rejection of AG '545.

6. Claims 2-9 and 11-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Soderlund (US 6,013,431).

Soderland teaches a method for detecting a target nucleic acid comprising:
(a) providing a detectable amount of a target nucleic acid polymer in a single stranded form,
(b) hybridizing the detectable amount of the nucleic acid polymer with one or more oligonucleotide primers (forming a primer-nucleic acid duplex), wherein each primer has a nucleotide sequence that is complementary to a sequence in the target nucleic acid polymer, such that when the primer is hybridized to the target nucleic acid polymer, the 3' end of the primer

binds to a nucleotide flanking the specific nucleotide at the defined site in the target nucleic acid (i.e. the first unpaired base immediately downstream of the 3' end of the primer), (c) exposing the hybridized nucleic acid polymer to a polymerization agent in a mixture containing at least one deoxynucleotide, said deoxynucleotide comprising a detectable label, and one or more chain terminating nucleotide analogues, such that a detectable primer extension product is formed if the labeled deoxynucleotide is complementary to the specific nucleotide at the defined site, and (d) analyzing the polymerization mixture of step (c) for the presence or absence of the primer extension product containing the labeled deoxynucleotide at the 3' end thereof, whereby the identity of the specific nucleotide at the defined site is determined (col. 18, ln. 19-53).

The reference also teaches that two or more differently labeled dNTPs (non-terminator nucleotides) can be added to the primer-nucleic acid duplex, wherein the detection is better interpreted by adding dNTPs that are different than the terminator nucleotide (col. 8, ln. 58-64). The reference also teaches the use of this invention with various labels such as radioactive or fluorescent labels (see examples 1-7, col. 9-18). The reference also teaches that the primer extension reaction can be performed by enzymatic means using template dependent enzymes (i.e. T7 DNA polymerase, T4 DNA polymerase, reverse transcriptase, etc.) (col. 8, ln. 10-17). The reference also teaches that the primer may contain an attachment moiety (i.e. biotin, antigens, etc.) (col. 6, ln. 16-31), that permits affinity separation of the from the unincorporated reagent and/or the nucleic acid of interest (col. 6, ln. 53 to col. 7, ln. 26), and furthermore, that a solid support may be used in the separation process (col. 6-7). The reference also teaches that the nucleic acid of interest can be any human, animal, plant, or microbe (col. 5, ln. 25-32).

Response to Applicants Arguments

The Soderland '431 patent entitled, "Method for determining specific nucleotide variations by primer extension in the presence of mixture of labeled nucleotides and terminators" is based on a method of determining unknown bases. Applicants patent application entitled, "Detection of sequence variation of nucleic acid by shifted termination analysis" also seeks to determine the identity of an unknown base at a predetermined location. These methods are general methods that are carried out when the specified base to be determined is unknown, which therefore, means that at the outset of the method, it is not clear as to which dNTP will be opposite the unknown nucleotide of interest. Thus, the outcome of what type or dNTP (or ddNTP) will not be known until the completion of the method. Whether or not there is or is not primer extension is based on this outcome, and therefore, primer extension is not specifically based on the method steps, but on a target by target specific basis (i.e. primer extension is based on the unknown base).

Applicants argue that Soderlund "fails to provide any disclosure or support for incorporating a plurality of labeled nucleotides to the primer to provide a strong signal". First, it is noted that the many of the claims only require a singly labeled non-terminator, not a plurality of labeled non-terminators. Regardless, Soderlund does teach the use of multiply labeled non-terminators:

> The detection step primer is annealed to the copies of the target nucleic acid and a solution containing one or more nucleoside triphosphates including **at least one labelled or modified nucleoside triphosphate**, is added together with a polymerizing agent in conditions favoring primer extension. (col. 7, ln. 49-53).

> Yet another possibility is to use **two or more different, differently labelled dNTPs** making it possible to detect heterozygotes in an undivided sample. (col. 8, ln. 58-60).

Applicants provide Exhibit A, which is alleged to describe a difference in the extension signal that "is noticeably powerful". However, this exhibit shows detection signals from a gel. First, it is noted that the claimed method specifically teaches away from using a gel to detect sequence variations. Additionally, exhibit A does not teach how the methods were carried out (i.e. method steps, labeling strategy, etc.), and does not provide any evidence to support Applicants contentions. Soderlund, at least, teaches several different labeling strategies (i.e. adding one or more labeled dNTPs), and it is not clear which of Soderlund numerous embodiments are demonstrated in exhibit A. It is also noted that Example 7 (col. 16-18), teaches the incorporation of 3 labeled dNTPs and one unlabeled ddNTP (col., 17, ln. 15-17).

For these reasons, and those of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 16-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Applied Genetics (WO 96/30545), as applied to claims 2-9, 11-15 and 23-37 above, and in further view of Shuber (US 5,888,778).

The teachings of Applied Genetics are presented above. Specifically, Applied Genetics teaches a method of detecting a target nucleic acid performing a primer extension reaction in the presence of three non-terminators (abstract, pgs. 16 and 58, Table 1A and B).

Applied Genetics fails to teach the method wherein the primer is immobilized on a solid phase.

Shuber teaches that nucleic acids (i.e. a primer) can be bound to solid-phase supports (col. 4, ln. 25-26). Shuber teaches that the immobilization of nucleic acids are advantageous for simultaneously processing and screening a large number of samples and controls, and thus facilitating analysis, and furthermore, solid-phase supports can be used in automated systems.

In view of the teachings of Shuber, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Applied Genetics so as to have immobilized a primer on a solid-phase, instead of carrying out the method in solution, in order to have achieved the benefits of using solid-phase supports as taught by Shuber of simultaneously processing and screening a large number of samples and controls, and thus facilitating analysis, and furthermore, that solid-phase supports can be used in automated systems.

Response to Applicants Arguments

Applicants argue that Shuber does not remedy the defects in AG '545. However, the alleged defects of AG '545 have been remedied above, in the response to Applicants arguments to the 102 rejection of AG '545. Therefore, this rejection is maintained.

Conclusion

9. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
January 17, 2003

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
1/21/03